Office Action Summary	Application No.	Applicant(s)
	10/633,629	RASHTCHIAN ET AL.
	Examiner	Art Unit
	ILEANA POPA	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-62* is/are rejected.

7)☒ Claim(s) *50, 51, 54, and 55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/21/2011 has been entered.

Claims 1-42 have been cancelled. Claims 43-62 are new.

Clams 43-62 are pending and under examination.

Claim Objections

2. Claims 50, 51, 54, and 55 are objected to because of the following informalities:

The claims recite IS20-US, FO-I 0, FO-10, and FG-IO. It is clear from the specification that these are typographical errors and that the applicant intended to claim 1520-US and FG-10 (see p. 6, last paragraph). Appropriate correction is required.

Claim Rejections - 35 USC § 112, 4th paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> Subject to the following paragraph, a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

4. Claims 48 and 62 are rejected under 35 U.S.C. 112, fourth paragraph, as failing to further limit the subject matter of claims 46 and 59, respectively. Specifically, claims 46 and 59 are drawn to a probe labeled with a detectable label. The fluorescent nucleic acid-binding dye recited in the dependent claims 48 and 62 is not a probe labeled with a detectable label.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 43-47, 52, and 56-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (Brain Research Protocols, 2000, 5: 211-217, of record), in view of both Lopez Garcia et al. (Analyst, 1991, 116: 517-520, of record) and Stemmer et al. (US Patent No. 5,834,252, of record).

Li et al. teach quantification of mRNA expression by TaqMan hot-start real-time RT-PCR, wherein the real-time RT-PCR is carried out in a MicroAmp Optical 96-well reaction plate to detect multiple target nucleic acids, wherein each well contains an aliquot of a master mix comprising Tween 20 and AmpliTaq Gold DNA polymerase (i.e., a thermostable polymerase), and wherein the amplified mRNA is optically detected (claims 43-47, 52, and 56-61) (Abstract; p. 212, column 1, Supply and reagents; p. 213, column 1 bridging column 2 and Fig. 1).

Li et al. do not teach including and anti-foam agent in their master mix (claims 43 and 52). However, doing such is suggested by the prior art. For example, Lopez Garcia et al. teach that the small air bubbles formed in the presence of detergents worsen the reproducibility of quantification by optical detection; Lopez Garcia et al. teach using anti-foam agents to overcome this problem (p. 518, column 1). Stemmer et al. teach that anti-foam agents could be used in PCR (i.e., the anti-foam agents do not substantially inhibit the polymerase) (column 10, lines 7-30). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Li et al. by further including an anti-foam agent in their master mix to achieve the predictable result of improving the reproducibility (i.e., accuracy) of optical detection in RT-PCR. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

7. Claims 43-48, 52, and 56-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. taken with both Lopez Garcia et al. and Stemmer et al., in further view of Blaschke et al. (J Immunol Methods, 2000, 246: 79-90).

The teachings of Li et al., Lopez Garcia et al., and Stemmer et al. are applied as above for claims 43-47, 52, and 56-61. Li et al., Lopez Garcia et al., and Stemmer et al. teach using TaqMan probes and not a fluorescent nucleic acid-binding dye (claims 48 and 62). Blaschke et al. teach that real-time RT-PCR can be performed by using either TaqMan probes or nucleic acid-binding dyes (p. 80, column 2, first paragraph, p. 82, column 1, second paragraph). It would have been obvious to one of skill in the art, at

the time the invention was made, to modify the method of Li et al., Lopez Garcia et al., and Stemmer et al. by replacing their TaqMan probe with a nucleic acid-binding dye to achieve the predictable result of quantifying the RT-PCR products. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

8. Claims 43-47, 49-52, and 56-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. taken with both Lopez Garcia et al. and Stemmer et al., in further view of each Kyle (US Patent No. 5,658,767; of record), Sigma catalog (1998, of record) and Wierenga (US Patent No. 5,968,889; of record).

The teachings of Li et al., Lopez Garcia et al., and Stemmer et al. are applied as above for claims 43-47, 52, and 56-61. Li et al., Lopez Garcia et al., and Stemmer et al. do not specifically teach using 1520-US as an anti-foam agent (claims 50, 51, 54, and 55). Kyle et al. teach the 1520-US as a suitable silicone-based anti-foaming agent (column 11, Example 3). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Stemmer et al. with 1520-US as an anti-foam agent to achieve the predictable result of improving the reproducibility (i.e., accuracy) of optical detection in RT-PCR.

Li et al., Lopez Garcia et al., Stemmer et al., and Kyle do not teach using two anti-foam agents (claims 49-51 and 53-55). However, doing such is suggested by the prior art. For example, the Sigma catalog teaches that anti-foaming agents can be supplied as a mixture of organic anti-foams and silicone-based anti-foams, and that O-30 is an organic antifoaming agent. Wierenga teaches that silicone-based anti-foaming

agents are not that effective, and that the addition of organic anti-foamers results in a synergistic anti-foaming combination (Abstract, column 1, lines 38-51, and also column bridging column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Li et al., Lopez Garcia et al., Stemmer et al., and Kyle by further adding an organic anti-foamer such as O-30, with a reasonable expectation of success. The motivation to do so is provided by Wierenga who teaches that the addition of organic anti-foamers to silicone-based anti-foamers results in a synergistic anti-foaming combination. One of skill in the art would have had a reasonable expectation of success in using such a combination because Sigma catalog describes such combinations and because the art teaches that such combinations are very efficient in controlling foam formation. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Most of the arguments are not new and were previously addressed. The new arguments are answered below in the order they were presented.

The applicant argues that none of the references addresses the requirement for detergent for polymerase stability.

In response, Li et al. do not have to specifically teach such. That detergents improve Taq stability was common knowledge in the art, as evidenced by Li et al. who teach a master mix comprising Tween 20 and Taq DNA polymerase and by the U.S. Patent No. 6,127,155 cited by the applicant.

The applicant argues that one of skill in the art would have had no motivation to add an anti-foam agent because it would have been expected that the anti-foam would counteracted the beneficial and necessary action of detergent.

This is not found persuasive because it is just an argument not supported by any evidence.

The applicant argues that the examiner has failed to identify a single reference teaching the use of antifoam in qRT-PCR.

This argument is not material to the instant obviousness-type rejection. If such a reference would have been identified, the claims would have been rejected as being anticipated and not as being obvious.

The applicant argues that Lopez Garcia teach that attempts to use a combination of detergent and antifoam failed because the presence of the detergent led to inaccurate and unreliable results. Thus, one of skill in the art would recognize that the presence of detergents and anti-foam could interfere with optical detection methods.

This is not found persuasive. The full passage from Lopez Garcia reads as follows:

> "When the surfactant concentration was higher than about 0.20%, the slurries gave rise to abundant foam and small air bubbles were trapped in the sample loop of the FI manifold, making the reproducibility worse. Although this problem could be overcome by adding a few drops of antifoaming agent [Antifoam A (Fluka)] to the slurry, it was also noted that Triton X-100 decreased the absorption signal for copper, both for aqueous solutions and slurries, and hence this surfactant was not employed."
> (p.518, column 1, second full paragraph)

It is perfectly clear from this passage that the use of antifoaming agents improves reproducibility and it is the detergent and not the combination of detergent and surfactant which decreases the absorption signal for copper. By reading Lopez Garcia, one of skill in the art would readily understand that antifoaming agents could be used to improve the accuracy and reproducibility of quantification by optical detection.

The applicant argues that the examiner ignores all parts of Stemmer that lead away from using antifoaming agents in PCR.

This is not found persuasive. A teaching away from the invention is a teaching which renders prior art unsatisfactory for the intended purpose (MPEP 2145 [R-6] X D). There is no teaching in the prior art as a whole (including in Stemmer) that antifoaming agents are not suitable to be used in PCR. Importantly, the prior art teaches using antifoaming agents in nucleic acid amplification reactions (see Durmowicz et al., U.S. Patent No. 5,962,273, of record). While Durmowicz et al. teach SDA and not PCR, one of skill in the art would recognize that if the use of an antifoam agent in a SDA reaction is successful, the use of an antifoaming agent in PCR, as taught by Stemmer, would have a reasonable expectation of success. Apart from an argument, the applicant did not present any evidence to the contrary. Based on the teachings in the art as a whole, one of skill in the art would have known that antifoam agents could be used in nucleic acid amplification reactions (including PCR) and would have been motivated to use such in order to improve PCR accuracy.

9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633